STUDY ON RELATIONSHIP BETWEEN SEVERITY OF PRE ECLAMPSIA AND URINE SPOT PROTEIN CREATINIE RATIO VERSUS URINE ALBUMIN AND MATERNAL AND FETAL OUTCOME

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CERTIFICATE

This is to certify that this dissertation titled "**STUDY ON RELATIONSHIP BETWEEN SEVERITY OF PREECLAMPSIA AND URINE SPOT PROTEIN CREATININE RATIO VERSUS URINE ALBUMIN AND MATERNAL AND FETAL OUTCOME**" is a bonafide record work done by **Dr.NIRANJANA ASOKAN** under the guidance and supervision in the Department of Obstetrics & Gynecology during the period of her post graduate study at Govt. Theni Medical College & Hospital, Theni for the degree of M.S (Branch II) **OBSTERICS & GYNECOLOGY** from July 2016 to June 2017.

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DECLARATION

I solemnly declare that the dissertation titled "**STUDY ON RELATIONSHIP BETWEEN SEVERITY OF PREECLAMPSIA AND URINE SPOTPROTEIN CREATININE RATIO VERSUS URINE ALBUMIN AND MATERNAL AND FETAL OUTCOME**" has been prepared by me.

This is submitted to **The Tamilnadu Dr.M.G.R Medical University**, Chennai in partial fulfillment of the requirements for the award of M.S Degree Examination (Obstetrics & gynecology) to be held in May 2018. This record of work has not been submitted previously by me for the award of any degree or diploma from any other university.

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CONTENTS

INTRODUCTION:

Pre eclampsia is a multisystem disorder characterized by hypertension and proteinuria. The incidence of pre eclampsia is about 10% which is a significant increase from 5-8% earlier[1]. It is an important contributor of maternal morbidity and mortality, responsible for about 16% of maternal deaths[6]. Likewise not just the mother, babies born to pre eclamptic mothers are at five times increased mortality risk.

Increased blood pressure of ≥140mm Hg of systolic BP and ≥90 mm Hg of diastolic Bp after 20 weeks of gestation measured 6 hours apart within a week is defined as hypertension complicating pregnancy. These women require laboratory evaluations of platelet count, renal function, liver function, proteinuria to assess and diagnose severity of pre eclampsia.

Proteinuria is now not considered significant criteria to define pre eclampsia. Yet the rising proteinuria can have an increased incidence of severe pre eclampsia and poorer outcomes. Hence the aim of management is to predict it early and thus prevent the poor outcome.

Pre eclamptic mothers with proteinuria tend to have poorer outcome as against the hypertension only group as evidenced by Chua S et al[2], 1992, Ferrazzani S[3], 1990, Brown M et al[4], 1996.

There are multiple methods to predict the severity of pre eclampsia such as

A.Calcium creatinine ratio

B. Serum uric acid

C. Serum LDH

D. 24 hour urine protein creatinine ratio

24 hour urine sample protein measurement is the standard method for detection ofseverity of pre eclampsia and proteinuria. 24 hour urine collection is inconvenient to the patient and is time consuming.

In this regard urine spot protein creatinine ratio is a simple alternative to assess proteinuria and predict severity of pre eclampsia. It is a test that can be performed at all health care facilities and is more economical as it does not require much technicalities. Wang M et al[5] found urine spot protein creatinine ratio to be as effective as 24 hour urine protein estimation in assessing significant proteinuria.

This urine spot PCR can assess proteinuria in non pregnant women also. International Society for Study of Hypertension in pregnancy, the Society of Obstetric medicine of Australia and New Zealand[7] have approved the urine spot PCR test in pregnancy to identify significant proteinuria (>0.3g/24hr).

Hence this study aims to study the efficacy of a simple urine spot protein creatinine ratio versus the urine albumin test in predicting the severity of pre eclampsia and their effect on maternal and fetal outcome.

AIMS AND OBJECTIVES:

To study the ability of urine spot protein creatinine ratio in predicting severity of pre eclampsia over urine albumin.

To study the effect of the severity of pre eclampsia on maternal and fetal outcome.

REVIEW OF LITERATURE:

PRE ECLAMPSIA IN HISTORY:

Pre eclampsia has been noted from ancient times. Even the ancient literature from India, Egypt, China notes that when a pregnant woman dies of convulsion, the in utero baby should be delivered by cesarean section.

Hippocrates reported that during pregnancy complicated by acute episode of convulsions can prove to be fatal to the mother.

Galen noted the occurrence of convulsions in pregnancy in the 2nd century AD.

In 1739, the convulsions occuring from eclampisa and epilepsy were found to be different by de sauvages.

In 1790, the term eclampsia was first coined by Bossier.

In 1918 Lahlein and in 1920 Fahr noted the changes in renal glomeruli occuring in women with pre eclampsia complicating pregnancies.

In 1959, glomerular capillary endotheliosis was demonstrated by Farguhar.

PRE ECLAMPSIA:

Pre eclampsia as noted all over the world as the common medical disorder complicating pregnancy and resulting in poor maternal and fetal morbidity and mortality. The incidence of pre eclampsia varies from 7 to 10%.

It is characterised by changes like:

1. Reduced plasma volume causing associated vasoconstriction
2. Activated coagulation cascade presenting as a hypercoaguable satte
3. Reduced trophoblastic invasion causing insufficiency
4. Loss of reduced vasopressor sensitivity presenting with active renin angiotensin response
5. Altered renal tubular function

All these changes are also characteristic of pre eclampsia proving hypertension is not the only diagnostic feature. These pathological changes are responsible for the poor outcome associated with pre eclampsia. Hence there occurs the need to identify the disease early and manage it to prevent its progre4ssion and thereby attempt to reduce the complications occuring to mother and fetus.

DEFINITION:

There have been many classification systems for pre eclampsia. This condition is now defined as presence of elevated systolic blood pressure more than 140mm Hg and diastolic pressure more than 90 mm Hg with associated proteinuria occuring

for the first time after 20 weeks of gestation in a women who was previously considered to be normotensive.

ACOG classification:

1. Gestational hypertension

   The occurrence of elevated systolic blood pressure more than 140mm Hg and diastolic blood pressure more than 90mm Hg measured 6 hours apart within a week for the first time after 20 weeks of gestation and returning to normotensive state within 6 weeks postpartum. Hence this is a retrospective diagnosis.

2. Pre eclampsia

   The features of elevated blood pressure with asscoiated significant proteinuria of more than 300mg in 24 hours, occuring first after 20 weeks of gestation.

   Non severe: 140-159/90-109mm Hg

   Severe: ≥160/110mm Hg

3. Eclampsia

The features of pre eclampsia associated with generalised tonic clonic convulsions in a women not known to be epileptic.

4. Chronic hypertension

   The elevated blood pressure status occuring before 20 weeks of gestation after ruling out multiple pregnancy, hydatiform mole, gestational trophoblastic diseases or pregnancy in a woman known to be hypertensive or on anti hypertensive medication.

5. Chronic hypertension with super imposed pre eclampsia

   Woman with history of hypertension that antedates pregnancy presenting with worsening of baseline laboratory investigations, or new onset proteinuria in woman with chronic hypertension.

   CRITERIA FOR SEVERE PRE ECLAMPSIA:

   - Systolic blood pressure >160mm Hg
   - Diastolic blood pressure >110mm Hg
   - Proteinuria >5gm/day
   - Oliguria <400ml/day
   - Neurological signs:

- Headache
- Visual disturbances
- Altered consciousness
- Epigastric pain
- Altered liver function tests
- Liver rupture/ subcapsular hematoma
- HELLP syndrome
- Pulmonary edema
- Thrombocytopenia <1 lakh/mm^3

The recent modifications in pre eclampsia diagnosis include removal of proteinuria in diagnostic criteria as it is a physiological condition, removal of edema from diagnosis as it is a physiological condition in pregnancy, using Korotkoff V instead of korotkoff IV for measuring diastolic BP due to reduced inter observer variation and reproducibility and better correlation with intra arterial pressure monitoring.

The earlier diagnosis of elevation of systolic blood pressure more than 30mm Hg and diastolic blood pressure more than 15mm Hg from the baseline is no longer used in definition of pre eclampsia.

In case of diastolic blood pressure >110mm Hg it can be classified as hypertensive crisis. When the systolic blood pressure is more than 170mm Hg, there is increased risk of poor outcome and risk of complications.

DELTA HYPERTENSION:

The cut off points of 140/90mm Hg was decided based on middle aged men. However young females can have a different cut off value. Their baseline blood pressure could be in the lower limit of normal and even with increase in blood pressure due to pre eclampsia they fail to record a blood pressure hgher than 140/90mm Hg. These women are diagnosed with blood pressure measurements around 25th centile for normal young, healthy, pregnant women. They develop acute rise in blood pressure less than 140/90mm Hg which is termed as delta hypertension.

ETIOPATHOGENESIS:

Pre eclampsia disorders are more likely when women

- Have chorioninc villi exposure for the first time as in primigravida
- Have exposure to excess of chorionic villi as in twin gestation or molar pregnancy

- Have medical comorbidities like diabetes, renal disorders or cardiovascular disorders that can cause activation of endothelial cells
- Have a genetic predisposition to pre eclampsia because of family history or children born to mothers with pre eclampsia

RISK FACTORS FOR PRE ECLAMPSIA:

MATERNAL RISK FACTORS:

- Primigravida
- Primiparity
- Advanced maternal age
- Teenage pregnancy
- History of pre eclampsia in previous pregnancy
- Obesity
- Associated medical conditions:
- Diabetes
- Antiphospholipid antibody syndrome
- Family history of pre eclampsia

PLACENTAL RISK FACTORS:

- Multiple pregnancy
- Hydatiform mole
- Triploidy
- Poor placentation
- Placental hydrops

Presence of fetus is not mandatory for developing pre eclampsia. The basic pathology in fetus is damage of vascular endothelium that leads on to vasospasm, causes plasma leakage and thromboembolic episodes.

TWO STAGE DISORDER:

The subtypes of pre eclampsia depend on remodeling of uterine spiral arteriole due to invasion of trophoblastic tissue. Ness and Roberts came up with the concept of maternal and placental pre eclampsia. Redman et al gave the stages of development of pre eclampsia.

Stage 1: Defective endovascular invasion by trophoblasts

Stage 2: Clinical syndrome of pre eclampsia

Recent studies show pre eclampsia to be a spectrum and not as stages

PATHOPHYSIOLOGY:

The basic underlying pathology of pre eclampsia is vasospasm. This pathology occurs due to poor placentation. Normally in pregnancy there occurs trophoblastic invasion of spiral arterioles making the placental circulation into a low resistance flow. This condition is considered to be specific to pregnancy. It does not require the presence of fetus as the basic pathology is due to placenta. This is the reason for pre eclampsia in hydatiform mole.

Due to poor placentation instead of low resistance flow, the vessels undergo vasospasm and results in uteroplacental insufficiency. This insufficient flow results in placental ischemia and hypoxia. The reason for this uteroplacental insufficiency is due to changes that occur in spiral arterioles are:

- Decreased trophoblastic infiltration in arterial walls during formation of placenta leading to high resistance flow
- Formation of atherosis – fibrin platelets, foam cells get aggregated in the arteries and resulting in blockage of the arteries either partially or completely.

ABNORMAL TROPHOBLASTIC INVASION:

Endovascular trophoblasts invade the spiral arterioles and replace the existing endothelial cells and thus increase the diameter of the vessels. There is only superficial invasion in the venous system. This remodeling of uterine spiral arterioles occur at the decidua basalis. In cases of pregnancy complicated by pre eclampsia there occurs incomplete invasion by the trophoblasts. Invasion occurs only till decidual vessels and not of the myometrial vessels. There appears to be a relationship between severity of pre eclampsia and the amount of trophoblastic invasion.[13]

This abnormal spiral arteriole will affect the placental blood flow. Thus abnormal placentation will predispose the mother to develop pre eclampsia, placental insufficiency, restricted growth in fetus, abruption placenta, preterm delivery.

IMMUNOLOGICAL FACTORS:

There occurs some degree of tolerance to placental and fetal antigens in the mother. When this is lost, maternal immune system reacts against the paternal antigens and result in pre eclampsia.[11]Pre eclampsia risk is increased when there is impairment to development of blocking antibodies to placental antigens. When there is increased paternal antigen exposure, the risk of pre eclampsia is also increased as in the case of molar pregnancies. Immune maladaptation theory shows that when there is reduced expression of the nonclassic HLA which is an

immunosuppressant on the extravillous trophoblasts there exists an increased risk for development of pre eclampsia.[12] Th1 cells are responsible for inflammatory cytokines whereas Th2 cells provide humoral immunity. When there is increased risk of pre eclampsia, Th1 action is increased and there is change in ratio of Th1/Th2.

ENDOTHELIAL CELL ACTIVATION:

The inflammatory maladaptation results in defective placentation, which leads to release of multiple factors from placental bed. These antiangiogenic and metabolic factors along with cytokines released from inflammatory maladaptation will result in injury of endothelial cells.[13] TNF α and IL cytokines cause oxidative stress associated with pre eclampsia and result in release of reactive oxygen species and free radicals that leads on to lipid peroxides. This cascade of events cause injury of endothelial cells, interfere with prostaglandin production and nitric oxide production, foam cells formation and end in atherosis. Atherosis activated the microvascular coagulation, affect the capillary permeability. The features of pre eclampsia like edema and proteinuria manifest.

NUTRITIONAL FACTORS:

Antioxidant rich foods like fruits result in decreased incidence of pre eclampsia.[14] Daily intake of ascorbic acid around 85gm decreases risk of pre eclampsia. Lower

intake of calcium, vitamin C, vitamin E have no effect on incidence of pre eclampsia.

GENETIC FACTORS:

There is a 20 to 40% risk of pre eclampsia in daughters born to pre eclamptic mothers. Monozygotic twins have 60% concordance. Various genes like MTHFR, F5, ACE, CTLA 4, LPL, SERPINE, HLA, NOS3 that have maternal and paternal inheritance are associated with increased risk of pre eclampsia. Genes for Fas factor, HIF protein, lymphotoxin, apoE, are also associated with risk of pre eclampsia.

SYSTEMIC EFFECTS OF PRE ECLAMPSIA:

Cardiovascular system:

Depending on severity of blood pressure, duration of the disease, pre eclampsia presents with increase in peripheral vascular resistance due to vasospasm. Hence these patients develop a hyperdynamic circulation due to fall in cardiac output. Due to protteinuria causing ddecreased oncotic pressure, and added alveolar endothelial - epithelial leak they can develop pulmonary edema.

Blood volume:

Pre eclamptic mothers have a decreased volume of blood in circulation. Due to vasoconstriction and endothelial activation, and plasma leakage they present with hemoconcentration instead of normal physiological hemodilution of pregnancy.

Coagulation:

Thrombocytopenia with platelet count less than 1 lakh/cu mm is a feature of severe pre eclampsia. Pre eclampsia also affects liver and manifests with reduced clotting factors, hemolysis that is identified by the rise in LDH, abnormal red blood cells o peripheral smear study, reticulocytosis. Hemolysis in pre eclampsia occurs because of the endothelial disruption and aggregation of platelets at sites of damaged endothelium resulting in microangiopathic hemolysis. Fall in fibrinogen and rise in fibrin degradation products can also manifest in patients with HELLP syndrome.

Placenta:

Due to uteroplacental insufficiency there can be infarcts in the placenta. Chorionic villi maybe congested, degenerations, syncytial knots, endothelial proliferation and calicification of villous spaces are other manifestations in the placenta due to pre eclampsia.

Kidneys:

Pre eclampsia presents with fall in renal perfusion and as a consequence in the glomerular filtration rate. But due to physiological rise in renal perfusion and glomerular filtration due to hemodilution of pregnancy, the effects of pre eclampsia maybe compensated and the values may present in the normal range albeit in the low level of normal.

The reduced filtration, leads to reduced excretion and elevated serum uric acid levels. Decreased calciuria occurs before of the tubular reabsorption of calcium. Proteinuria develops.

Acute renal failure a dreaded complication of pre eclampsia occurs due to tubular necrosis due to hypotension and hypovolemia brought on by hemorrhage which is poorly tolerated in pre eclamptic women because of decreased blood volume. But this renal failure of pre eclampsia is reversible.

Glomerular endotheliosis is a hallmark of pre eclampsia wherein there occurs endothelial cell hyperplasia and foamy macrophages, lymphocytes in the lumen of glomerular capillaries and mesangium. Early focal segmental glomerulosclerosis is another feature that develops in some of the pre eclamptic patients. All these lesions resolve with termination of pregnancy.

Liver:

Infarction and subcapsular hemorrhage occur in the liver causing stretching of Glissons capsule which manifests with epigastric pain, elevated serum transaminases. These hemorrhages get organized into hematomas that can finally present with liver rupture.

Brain:

Cerebral arteriolar vasospasm due to auto regulation of the hypertension results in ischemia, infarction and edema of brain tissue. Following this there occurs compensatory dilation resulting in hyperperfusion. So brain presents with edema in pre eclamptic women. This cerebral edema manifests as altered mental status and gradually progresses to supratentorial herniation. Following edema, cerebral hemorrhage can occur and present with hemiplegia, visual disturbances, diplopia, scotoma. Blindness in pre eclampsia occurs due to papiledema, occipital lobe lesions, PRES. All of the conditions resolve with termination of pregnancy and blindness becomes reversible.

Vascular system:

In cases of severe pre eclampsia, there can be features of disseminated intravascular coagulation due to arteriolar thrombi causing ischemia, necrosis and hemorrhage. Acute left ventricular failure occurs due to subendocardial petechial hemorrhages. Adrenal glands may develop hemorrhage and necrosis.

Pre eclampsia is a common medical disorder of pregnancy that causes increased hospital admissions, maternal mortality and morbidity, and perinatal morbidity. The aim of management of pre eclampsia is to diagnose the condition early, predict the severity and provide effective management to reduce the mortality.

Reproduction:

Uteroplacental insufficiency affects in utero growth of fetus causing IUGR babies, preterm deliveries that maybe spontaneous or iatrogenic, compensatd placenta has high risk to develop abruption, that can lead on to fetal demise following abruption placenta, oligohydramnios or Doppler abnormalities.

PREDICTION OF PRE ECLAMPSIA:

- Mean second trimester blood pressure

  Absence of fall in blood pressure that normally occurs in mid pregnancy.

- Roll over test

- 24 hour ambulatory BP monitoring

- Angiotensin II

  Pregnancy due to trophoblastic invasion makes the vessels insensitive to the pressor effects of rennin angiotensin system. In pre eclamptic women, the

angiotensin pressor effect is retained and is marked rise in vasoconstriction following infusion of angiotensin.

- Fetoplacental AFP measurement
- Biochemical estimation:

  βhCG, inhibin A, PAPP –A, sFlt – 1, Activin A, ADAM12, P selectin are markers to predict pre eclampsia. Testing for these markers are done in first trimester.

- Serum uric acid estimation
- Microalbuminuria
- Antiphospsholipid antibodies
- BMI > 35kg/m^2
- Uterine artery Doppler

  Uterine artery blood flow impedance is reduced in pregnancy due to hemodilution. But due to decreased trophoblastic invasion in pre eclampsia there occurs a state of high impedance flow. Doppler ultrasound of these high impredance flow in uterine artery manifests as increased resistance with

diastolic notching. Pulsatility index and resistance index with diastolic notching are predictors of pre eclampsia.

Despite multiple screening tests devised to predict pre eclampsia, no single test in reliable for this purpose. The increased risk of complications and possibility of better outcome with early management of pre eclampsia makes the need for a reliable screening test all the more essential.

PROTEINURIA:

Normal women do not have proteinuria. Pregnancy despite having increased glomerular filtration and renal perfusion does not present with proteinuria. Hence presence of proteinuria can be used as a marker of renal impairment. The pathophysiology of pre eclampsia causes renal damage due to disease process causing capillary leak at the glomerular basement membrane. So hypertension and proteinuria become the defining features to differentiate pre eclampsia from gestational hypertension. Being an important association with pre eclampsia, proteinuria can also be used as a prognostic factor to predict the maternal and fetal outcome in pre eclampsia complicating pregnancies.

Stetler et al found that when proteinuria was diagnosed in pregnancy 62% of these women later developed pre eclampsia and had adverse outcomes. They constituted the high risk group.

The gold standard for assessment of proteinuria is 24 hour urine protein collection. But it is difficult to perform. The alternative option is urine spot protein creatinine ratio which is highly accurate, provides results that are reproducible, and has the advantage of being a convenient procedure over 24 hour urine collection.

There are many studies with urine protein creatinine ratio, each with different cut offs in different units like mg/mmol, mg/g, g/g. Published guidelines suggest a cut off ratio for urine spot protein creatinine ratio of 30mg/mmol. Brown et al study[8] showed that this cut off had a better negative predictive value than positive predictive value implying that when the spot protein creatinine ratio is less than 30mg/mmol, there is less likely chance of patient being pre eclamptic.

Various meta analysis have been conducted to test the efficacy of this cut off ratio. A urin spot protein creatinine ratio of 0.30 to 0.35 is found to have 75% sensitivity and 75% specificity. Methven et al[9] showed that protein creatinine ratio was specific to detect proteinuria of more than 0.5-1g/day even in non pregnant people with chronic kidney disease. This proves the efficacy of this test in predicting proteinuria occuring due to all causes.

Proteinuria is normally present in pregnancy. But the associated damages caused by pre eclampisa like glomerular endotheliosis, ncresed leakage at glomerular capillary membrane, impaired renal function, loss of tubular reabsorption and

glomerular filtration, reduced clearance of uric acid causing hyperuricemic state affecting the tubular function result in increased proteinuria. When this levels of protein in urine amount to more than 300mg/24 hours urine the outcome of pregnancy worsens.

Increased protein or albumin excretion occurs in pre eclampsia, diabetic nephropathy, nephrotoxicity, hypertension, and drugs. Hence urine protein creatinine ratio can be useed as a reliable screening test to identify proteinuruia and therbey allow early diagnosis of pre eclampsia.

TESTS FOR PROTEINURIA:

Fresh samples of urine collected in a clean container are pre requisite for proteinuria estimation. Contaminated samples can give false values affecting the purpose of testing. Dilution of urine by intake of large amounts of fluid prior to testing is not advisable as it may also result in false low values of protein estimation.

- Dipstick test

  Dipstick coated with reagent material are used for estimation. Depending on the colour change proteinuria maybe assessed quantitatively.

  Trace – 0.1g/l

1+ 0.2g/l

2+ 1g/l

3+ 3g/l

4+ 10g/l

- Sulphosalicylic acid testing

  20% sulphosalicyclic acid is added in drops to urine in a test tube and turbidty is assessed.

  Trace – Cloudiness visible only against dark background

  1+ Cloudy, not flocculent, able to visualize the background

  2+ Cloudy granular, with haziness of background

  3+ Thick flocculent

  4+ Solid mass

- 24 hours urine protein estimation

  Collection of urine in a clean container for 24 hours and assess the amount of protein excreted. This test also allows us to estimate urine output and rule out oliguria.

GUIDELINES ON PROTEINURIA ESTIMATION:

NICE guidelines:

- Dipstick universal screening for proteinuria
- Reports of >1+ - confirmation with 24 hour urine protein estimation or spot PCR
- Reports of 300mg/24 hour, spot protein creatinine ratio >30mg/mmol is significant.

RCOG guidelines:

Proteinuria >2+ on dipstick needs confirmation and further evaluation.

STUDIES ON PROTIENURIA IN PRE ECLAMPSIA:

In a study conducted by Ivanov et al among 544 pregnant women, proteinuria was assessed both qualitatively and quantitatively. The results of this study showed that significant proteinuria had increased risk of fetal growth restriction, low birth weight babies, low Apgar score. This shows the prognostic efficacy of proteinuria in predicting fetal outcome.

Chan P et al conducted a retrospective study among a sample size of 321 women with pre eclampsia and proteinuria and reported that when the urine spot protein

creatinine ratio was more than 9g/day there was increased risk of adverse pregnancy outcome.

Wang M et al concluded that urine spot protein creatinine ratio can be used as an effective alternative to 24 hour urine protein in assessment of proteinuria.

Yamasmit et al performed a prospective study over a sample size of 42 patients and found that a cut off of >0.3 urine protein creatiinine ratio gave an accurate prediction of severity of pre eclampsia.

Buchinder et al conducted a study comparing the outcome of babies born to mothers with mild and severe pre eclampsia. They reported that severe pre eclampsia had a greater risk of poorer perinatal outcome.

Shiraz et al used calcium creatinine ratio to predict the severity of pre eclampsia. This test was based on the fact that in pre eclampsia due to tubular leak, urine calcium excretion is decreased and hypocalciuric state sets in. The results of this study was that calcium creatinine rario can effectively predict severe pre eclampsia.

A study conducted by Newman et al at USA among a group of 377 patients found rising proteinuria had association with earlier onset of pre eclampsia, severity of pre eclampsia, premature deliveries. The spectrum of pre eclampsia associated complications worsened as the titres of proteinuria rose.

Al Muhim et al study was conducted among 685 women. This was a retrospective study that reported greater incidence of pre eclampsia of around 40% among women <20 yrs and >40yrs of age. 30.2% of pre eclamptic mothers delivered at <37 weeks of gestation. The common complications encountered in the study group were abruptio placenta in 12.6%, oliguria in 7.9%, coagulopathy in 6% and renal failure in 4.1%. They also reported adverse perinatal outcome in the form of 2.34% stillbirths and 1.02% early neonatal deaths. The association between stillbirths and severe pre eclampsia was found to be significant.

Witlin AG, Sibai BM et al performed a study among women with severe pre eclampsia and eclampsia. These women mostly delivered at 24 to 33 weeks of gestation either vaginally or by cesarean. The outcomes analysed were intra uterine growth restriction and respiratory distress syndrome. They found that with advancing gestational age, there was worsening of severity of pre eclampsia and rise in incidence of intra uterine growth restriction. This growth restriction was found to be an independent prognostic factor for survival of these preterm babies. Respiratory distress was found to be improve with advancing gestational age of the babies.

Ferrazzani, Macuso et al conducted a study Catholic University, Italy. This study was conducted among 444 women. This study aimed to identify the effect of pre eclampsia on outcome of the pregnancy. The patients were grouped according to

the pre eclampsia classification into three groups namely, chronic hypertension, gestational hypertension, proteinuric pre eclampsia. This study reported that when there was significant proteinuria >0.3g/L patients were grouped in the third group. It was this group that presented with poor pregnancy outcome. The incidence of low birth weight and small for gestational age babies were more among the third group of patients. Likewise even the perinatal outcome was worse in the third group because there was a fourfold rise in perinatal mortality in the third group compared to other groups.

Jaschevatsky et al performed a study where the urine spot protein creatinine ratio was estimated among healthy pregnant women and pregnant women with pre eclampsia. The results of this study showed that women with pre eclampsia had higher values of urine spot protein creatinine ratio. This proves the efficacy of urine spot protein creatinine ratio in predictine the diagnosis of pre eclampsia and severity of pre eclampsia.

Phelon LK, Brown MA, Davis GK, Mangos G performed a prospective study to assess the dip stick urine analysis in diagnosing pre eclampsia. The study sample was 170 pregnant women with hypertension. This study compared dipstick urine analysis versus urine spot protein creatinine ratio. The study reported a 7% false positive rate with 3+ urine albumin report and 71% false positive diagnosis of pre eclampsia with 1+ urine albumin report. The results of this study showed that when

a cut off of urine albumin at 2+ was used to diagnnose pre eclampsia there was a better accuracy in diagnosing pre eclampsia. In order to avoid a false diagnosis of pre eclampsia the urine albumin test needs to be verified with a second test like urine spot protein creatinine ratio for diagnosing preegnant women with hypertension.

Hsu CD, Lucas Rb Chan DW studied the effect of increased urine thrombomodulin/ creatinine ratio in diagnosing the severity of pre eclampsia.The reports showed that women with pre eclampsia had a increased urine thrombomodulin/creatinine ratio when compared with women without pre eclampsia. A significant increase in urine thrombomodulin/ creatinine ratio was present in patients with severe pre eclampsia when compared to womoen with mild pre eclampsia.

Millar JC, Campbell SK, Higgins Br studied the predictive value of random urine kallikrein/ creatinine ratio in the prediction of pre eclampsia with proteinuria. The study sample included 370 patients. The results of this study showed urine kallikrein/ creatinine ratio to be a sensitive and specific predictor of pre eclampsia on par with other tests.

Sheshadri L, Venkatraman I studied the maternal and perinatal outcome in pre eclamptic pregnancies complicated with proteinuria and without proteinuria. The

study sample included 216 women with hypertension complicating pregnancy. The study duration was 18 months. The reports of the study showed poorer perinatal outcome in women with proteinuria proving proteinuria as a significant poor prognostic marker. Hence women without proteinuria did not have significant high risk or poor prognosis and can be managed in out patient basis without the need for hospitalisation.

MANAGEMENT:

PREVENTION:

Low salt diet:

This was advised earlier to reduce pre eclampsia. The recent guidelines issued following a randomized study reveal no benefit. NICE guidelines now advise against salt restrictions.

Calcium supplementation:

Studies showed increased incidence of pre eclampsia in women with low dietary calcium. Patrelli[15] et al showed pre eclampsia risk is lowered with increase in calcium intake. The recent guidelines show need for calcium supplementation only in women who have calcium deficiency.

Fish oil supplementation:

Eicosapentanoic acids, alpha linoleic acid, docosahexanoic acid are cardioprotective fatty acids that are found in fishes. Being cardioprotective they were believed to reduce atherosis and thereby also reduce pre eclampsia. Recent studies have showed no such benefit.

Exercise:

Kasawara[16] et al studied the effect of exercise on pre eclampsia and reported that there is a reduction in risk of pre eclampsia with exercise.

Antioxidants:

The pathogenesis of pre eclampsia points to imbalance in oxidant and anti oxidant activity. Decreased levels of anti oxidants was found in women with pre eclampsia. Meta analysis conducted by De-Regil showed no benefits in supplementing the anti oxidants[17]. Statins stimulate hemooxygenase which in turn inhibits release of sFlt 1 thereby preventing pre eclampsia.

Anti thrombotic agents:

Aspirin is used prophylactically in early gestation in preeclampsia complicating pregnancies to prevent atherosis and uteroplacental insufficiency and improve maternal and fetal outcome.

ANTIHYPRETENSIVES:

The primary aim of administering antihypertensives is to prevent cerebrovascular accidents.

The first line drug in preeclampsia is labetalol. It is a beta blocker used to treat mild to moderate hypertension. In cases of severe hypertension, labetalol is administered intravenously at doses of 10-20mg followed by 20-80mg every 30 minutes upto a maximum dose of 300mg. It can also be given as infusion at the rate of 1-2mg/min. The amin side effects of labetalol are hypotension and bradycardia.

Nifedipine is a calcium channel blocker used as 10mg tablet three to four times a day to a maximum dose of 120mg/day. It is a short acting drug that is administered when blood pressure is uncontrolled with labetalol alone or when the hypertension is severe.

Diuretics that are otherwise used to treat hypertension are contraindicated as first line therapy during pregnancy. They are indicated only in cases of congestive cardiac failure, pulmonary edema, renal failure. Diuretics are not advisable routinely in pregnancy because they reduce the intravascular volume and worsen the placental insufficiency due to preeclampsia and lead on to poor maternal and fetal outcome.

TERMINATION OF PREGNANCY:

Definitive management of preeclampsia is termination of pregnancy. Termination of pregnancy is offered at 37 weeks of gestation in non severe preeclampsia and 34 completed weeks in severe preeclampsia.

Mild hypertension requires blood pressure monitoring, twice weekly outpatient visit at antenatal clinic. There happens to be no role for salt and fluid restriction. Physical activity has to be reduced. Expectant management on outpatient basis can be continued as long as there is only mild elevation of pressure.

Severe hypertension presenting with any criteris as mentioned earlier needs admission and evaluation. They need to be administered antihypertensives to prevent occurrence of stroke. Immediate termination after patient is stable is advised when the patient is less than 24 weeks or more than 34 weeks of gestation. Expectant management with antenatal steroids are advised when the patient is in 24 to 34 weeks of gestation.

Mother needs to be monitored with 6^{th} hourly blood pressure monitoring, daily urine albumin, twice a week laboratory investigations and ophthalmic examination. Fetal surveillance to be done with ultrasound to monitor growth, twice weekly NST, weekly biophysical profile, periodic assessment of AFI, Doppler velocimetry

at 28 to 30 weeks to assess fetal growth restriction and decide timing of delivery. Doppler to be repeated at intervals of 2 to 4 weeks.

MODE OF DELIVERY:

Vaginal delivery is preferable depending on favourability of cervix. Ceasrean section is indicated in conditions like abruption, fetal distress, malpresentation and severe preeclampsia remote from term. It is not advisable to delay delivery more than 24 hours after induction.

FOLLOW UP:

Women with preeclampsia need to have blood pressure monitoring as they have increased chance of high blood pressure later on in life. The risk of recurrence of preeclampsia in future pregnancies is around 16%.

MATERIALS AND METHODS:

Study design: Prospective observational study

Study place: Department of Obstetrics and Gynecology, Govt Theni Medical College

Study duration: July 2016 and June 2017 (12 months)

Study sample: 300 patients

The study was conducted after approval from ethical committee. Informed written consent from all patients recruited in this study.

INCLUSION CRITERIA:

- Patients with ≥140/90mm Hg blood pressure
- Singleton pregnancy
- > 20 weeks GA
- Significant proteinuria (>2+ urine albumin on dipstick)
- Presenting with complications associated with pre eclampsia
- Chronic hypertension with superimposed pre eclampsia

EXCLUSION CRITERIA:

- <20 weeks GA
- History of hypertension before pregnancy
- Known renal disorder
- Known adrenal disorder
- Known history of epilepsy
- Multiple pregnancies
- Hydatiform mole
- Mothers not willing for study

METHOD:

Pregnant women found to have elevated blood pressure on their routine antenatal visit or those referred from PHC's as a case of PIH for evaluation to Govt Theni Medical College and Hospital were included in the study. The patients included in this study were those found to be hypertensive after 20 weeks of GA and not on any anti hypertensive drug prior to conception. Patients with chronic hypertension with superimposed pre eclampsia were also included in the study.

The women thus selected were then admitted for evalution of pre eclampsia. The blood pressure was recorded after 30 minutes rest in sitting posture in the right arm

at the level of heart using a mercury sphygmomanometer. After 6 hours the blood pressure was checked again. Only women who presented with elevated blood pressure on second reading were included in the study.

The pateints selected to participate in the study were explained about the study, the risks of pre eclampsia and written informed consent for the willingness to aprticipate in the study was obtained.

These women who constitute the study sample were managed with 6^{th} hourly BP monitoring. They were then instructed to obtain a random midstream urine sample in a clean testing tube. This urine sample was sent to laboratory for estimation of proteinuira. Proteinuria estimation was done by dipstick method for urine albumin and urine spot protein creatinine ratio.

The patients wee also subjected to other hematological investigations to find the hematocrit, platelet concentration, liver function tests, renal function tests. They were also subjected to tests of end organ damage like fundus examination to identify hypertensive retinopathy changes, ECG and ECHO to identify any cardiac abnormalities, 24 hour urine protein when the assessed proteinuria is high or pre eclampsia is very severe. Intake output charts were maintained to prevent any occurrence of fluid overload.

After evaluating with laboratory investigations they were managed with anti hypertensives according to their blood pressure. The first line drug used to treat hypertension was Tab.labetalol 100mg in a bd dosage. In cases of severe pre eclampsia, Labetalol was supplemented with Tab.Nifedipine 10mg tds dosage. Patients who presented with uncontrolled hypertension with two drugs were then administered intravenous labetalol in 20mg bolus dose as and when required with careful blood pressure and cardiac monitoring.

All women included in the study were followed till delivery. Those of whose blood pressure was controlled and in early periods of gestation were discharged and followed up on outpatient basis till delivery. As the study was conducted mostly among women in later periods of gestation, there was no loss to follow up.

During the period of study, the factors for severity of pre eclampsia followed up include:

- Severe hypertension
- Placental abruption
- Renal failure with elevated urea, creatinine levels, or oliguria
- Liver damage in the form of elevated transaminases
- Fall in platelet count

- Occurrence of papilledema
- Occurrence of imminent symptoms like headache, visual disturbances, epigastric pain
- Occurrence of seizures

Apart from these factors maternal outcome was also assessed on the basis of :

- Duration of hospital stay
- Occurrence of HELLP
- Occurrence of postpartum eclampsia
- Occurrence of postpartum cardiomyopathy
- Occurrence of CVT

The factors used for assessing the fetal outcome included:

- Birth weight of the baby
- Gestational age of termination
- Stillbirths and sudden intrauterine death
- APGAR score
- Need for NICU admission

The study was thus completed after assessing the study sample with various outcome factors.

RESULTS:

The results of this study are tabulated as follows.

Table 1: Age distribution (n-300)

Age	No of cases	Percentage
<20yrs	49	16.3%
20-24 yrs	148	49.4%
25-29 yrs	73	24.3%
30-35 yrs	30	10%

As evidenced by this study the majority of women with pre eclampsia (49.4%) fell in the age group of 20-24 yrs.

26.3% of cases occurred among women <20yrs and >30yrs age group

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TABLE 2: Parity status (n-300)

Gravida	No of cases	Percentage
Primi	182	60.6%
G2	63	21%
G3	36	12%
G4	19	6.4%

Most of the cases in the study group were primigravida exposed to placental tissues for the first time.

39.4% cases occurred in multigravida women.

TABLE 3: Booking status (n-300)

Booking status	No of cases	Percentage
<4 visits	46	15.3%
4-9 visits	138	46%
>9 visits	116	38.7%

This study reported 15% prevalence of pre eclampsaia among women who were unbooked or had less than 4 antenatal visits.

TABLE 4: Socioeconomic status (n-300)

Socioeconomic status	No of cases	Percentage
Class 1	-	-
Class 2	6	2%
Class 3	42	14%
Class 4	111	37%
Class 5	141	47%

47% cases occurred in women belonging to socioeconomic class 5. 2% cases occurred in socioeconomic class 2. This disparity can be accounted to the fact that majority of patients attending the hospital belong to socioeconomic class 4 and 5.

TABLE 5: Gestational age at delivery (n-300)

Gestational age	No of cases	Percentage
$20\text{-}27^{+6}$ weeks	25	8.4%
$28\text{-}33^{+6}$ weeks	80	26.6%
34-37 weeks	156	52%
>37 weeks	39	13%

The majority of cases in the study group were in the gestational age of 34 to 37 weeks. (52%)

8.4% cases in second trimester.

26.6% cases in early preterm period.

TABLE 6: Type of pre eclampsia (n-300)

Types of pre eclampsia	No of cases	Percentage
Non severe pre eclampsia	181	60.3%
Severe pre eclampsia	91	30.4%
Eclampsia	20	6.6%
Chronic hypertension with superimposed pre eclampsia	8	2.7%

60.3% cases were diagnosed to have non severe pre eclampsia.

30.4% had severe pre eclampsia and 6.6% had eclampsia.

TABLE 7: Nature of treatment (n-300)

Treatment	No of cases	Percentage
Single anti hypertensive	150	50%
Double anti hypertensive	95	31.3%
MgSO4 regimen	55	18.3%

50% cases were on single hypertensive.

31.3% cases were on two anti hypertensive drugs.

18.3% cases needed Magnesium sulphate in view of eclampsia and imminent eclampsia.

TABLE 8: Degree of proteinuria (n-300)

Degree of proteinuria	No of cases	Percentage
Nil	25	8.3%
1+	78	26%
2+	129	43%
3+	53	17.7%
4+	15	5%

34.3% patients had insignificant proteinuria.

65.7% patients had urine albumin more than 2+ on dipstick.

TABLE 9: Spot urine protein creatinine ratio (n-300)

Spot PCR	No of cases	Percentage
<30	30	10%
30-100	187	62.4%
>100	83	27.6%

10% cases had insignificant urine spot PCR.

90% cases had significant proteinuria in spot PCR.

TABLE 10: Urine albumin vs urine spot PCR

Urine albumin	Spot PCR					Total
	<10	11- 20	30 -100	101 -200	>200	
0	9	11	4	1	0	25
1+	2	7	57	7	5	78
2+	0	0	97	29	3	129
3+	1	0	27	22	3	53
4+	0	0	3	6	6	15
Total	12	18	188	65	17	300

Kappa agreement statistics=0.21 fair correlation; Extended McNemars test =74.23 P=0.001

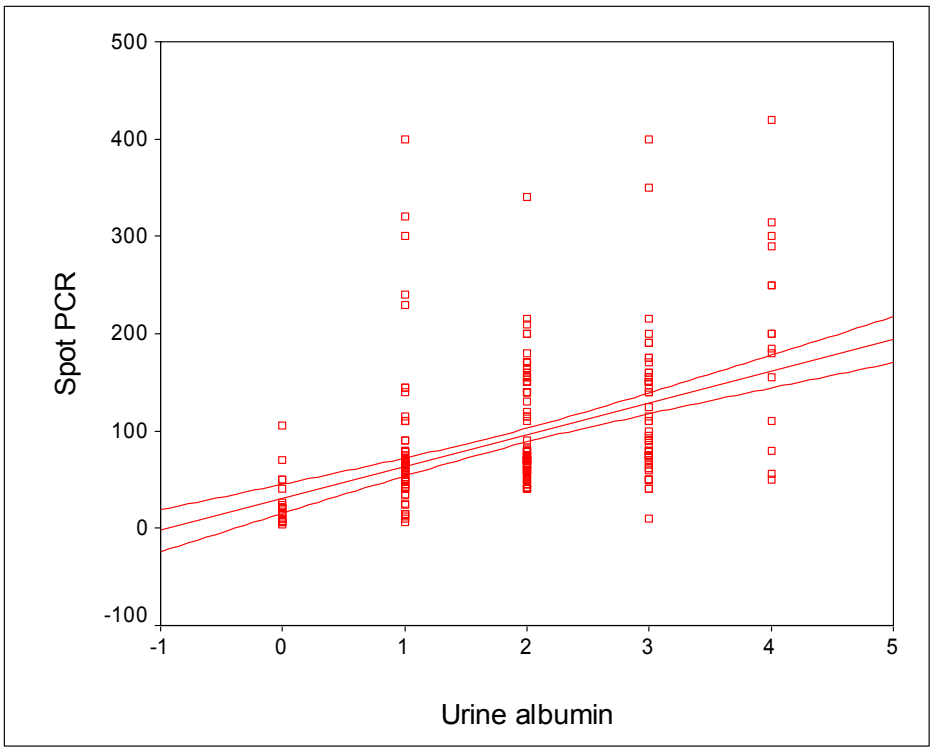

TABLE 11: Urine spot PCR versus Urine albumin in severity of pre eclampsia

Pre eclampsia	Number	Spot PCR >0.3	%	Urine albumin >2+	%
Non severe pre eclampsia	181	153	84.5%	101	56.4%
Severe pre eclampsia	91	91	100%	67	73.6%
Eclampsia	20	20	100%	15	75%
Chronic hypertension with superimposed pre eclampsia	8	6	75%	4	50%

TABLE 12:Urine albumin versus urine spot PCR in predicting severity of preeclampisa

Pre eclampsia	Number	Urine Spot PCR >0.3	%	Urine albumin >2+	%	Proportion test
Non severe pre eclampsia	181	153	84.5%	102	56.4 %	Z=5.87 P=0.01** (S)
Severe pre eclampsia	91	91	100%	67	73.6 %	Z=6.29 P=0.01** (S)
Eclampsia	20	20	100%	15	75%	Z=2.86 P=0.01** (S)
Chronic hypertension with superimposed pre eclampsia	8	6	75%	4	50%	Z=1.02 P=0.30 (NS)

** P<0.01 highly significant P>0.05 not significant

TABLE 13: Mode of delivery (N – 300)

Mode of delivery	No of cases	Percentage
Labour natural	121	40.4%
Abortions	25	8.3%
Operative vaginal	7	2.7%
LSCS	147	48.6%

8.3% cases aborted due to pre eclampsia and other causes.

43.1% cases delivered vaginally.

48.6% cases delivered by cesarean.

TABLE 14: LN versus LSCS (n-275)

	LN	Percentage	LSCS	Percentage
28-34 wks (80)	60	75%	20	25%
34-37 wks (156)	48	30.8%	108	69.2%
Term (39)	10	25.6%	21	53.9%

60% of preterm deliveries were vaginal.

69.2% of late preterm deliveries were cesarean.

53.9% of term deliveries were cesarean.

TABLE 15: Indications of abortion (n-25)

Indication	No of cases	Percentage
Eclampsia	8	32%
Severe preeclampsia	9	36%
Maternal Complications	3	12%
Obstetric causes	5	20%

8.3% of total cases underwent abortion.

20% abortions for obstetric causes.

32% abortions for eclampsia.

80% abortions were due to preeclampsia.

TABLE 16: Onset of labour (N-160)

Onset of labour	No of cases	Percentage
Spontaneous	55	34.7%
ARM & Syntocin	40	24.9%
Prostaglandin gel	65	40.4%

34.7% cases went into labour spontaneously.

40.4% cases were induced with prostaglandin gel.

TABLE 17: Indications for induction (n-105)

Indications	No of cases	Percentage
Severe preeclampsia	34	32.3%
Oligohydramnios	19	18.1%
Abruption	17	16.2%
PROM	10	9.5%
IUGR	8	7.6%
IUD	7	6.8%
Term	6	5.7%
Eclampsia	4	3.8%

TABLE 18: Indications for LSCS (N- 147)

Indications	No of cases	Percentage
Previous LSCS	44	30%
Failed induction	32	21.7%
CPD	30	20.4%
Abruption	16	10.8%
IUGR	11	7.5%
Fetal distress	10	6.8%
Breech	2	1.4%
AP eclampsia	2	1.4%

TABLE 19: Maternal outcome (n-300)

Complications	No of cases	Percentage
Abruption	40	13.3%
AP eclampsia	20	6.7%
HELLP	5	1.6%
PP Eclampsia	5	1.6%
CVT	5	1.6%
ARF	4	1.3%
Pulmonary edema	4	1.3%
PPCM	3	1%
PRES	1	0.3%
DVT	1	0.3%
Uncomplicated	212	70.7%

TABLE 20: Complications and association with urine albumin versus urine spot PCR

Complications	30-100	>100	%	Urine albumin 2+	Urine albumin 3+	Urine albumin 4+	%
Abruption	9	31	100	15	12	9	90
AP eclampsia	-	20	100	9	4	2	75
HELLP	4	1	100	-	2	-	40
PP Eclampsia	1	4	100	1	1	-	40
CVT	3	2	100	2	1	-	60
ARF	3	1	100	1	1	1	75
Pulmonary edema	3	1	100	3	1	-	100
PPCM	2	-	66.7	-	-	-	0
PRES	1	-	100	1	-	-	100
DVT	1	-	100	-	-	-	0

TABLE 21: Fetal outcome (n-275)

Fetal outcome	No of cases	Percentage
IUD	10	3.6%
IUGR	30	10.9%
Fetal distress	31	11.2%
Prematurity	47	16.7%
Mortality	42	15.65%

TABLE 22: Fetal outcome and association with urine albumin versus urine spot PCR

Complications	Urine spot PCR <30	30-100	>100	%	Urine albumin 2+	Urine albumin 3+	Urine albumin 4+	%
IUD	-	6	4	100	3	1	1	50
IUGR	-	24	6	100	16	8	-	80
Fetal distress	5	18	8	83.8	17	2	-	61.2
Prematurity	-	31	16	100	29	10	-	83
Mortality	1	18	23	97.6	15	10	9	81

TABLE 23: Birth weight of babies

Birth weight	No of cases	Percentage
<1 kg	25	8.3%
1-2 kg	65	21.7%
2-3 kg	162	54%
>3kg	48	16%

TABLE 24: NICU ADMISSION (N-155)

	No of cases	Percentage
Prematurity	45	29.1%
RDS	40	25.9%
LBW	55	35.4%
Birth asphyxia	15	9.6%

TABLE 25:Urine albumin Vs Spot PCR

		Spot PCR		
		<100	≥100	Total
Urine albumin	<2+	90	13	103
	≥2+	127	70	197
Total		217	83	300

	Estimate	95% CI
Sensitivity	87%	79% -93%
Specificity	35%	29% -43%
Efficiency	53%	47% -59%

False positive rate	64%	57% - 71%
False negative rate	12%	06% -21%
Kappa agreement	κ=0.18	sight agreement
McNemar test	χ2=92.83	P=0.001 significant

DISCUSSION:

Proteinuria is always tested in pre eclamptic patients with 24 hour urine protein estimation being considered the gold standard. But it may not always be performed correctly and results in a delay for collection and reporting. Spot urine protein creatinine ratio was chosen as an alternative to this because of it being accurate, reproducible, and convenient.

Hypertensive disorders are believed to occur in 5 to 10% of pregnancies.

The results of this study showed that common incidence of pre eclampsia occurred in women aged 20-24yrs. This is similar to worldwide incidence of pre eclampsia being more common among women belonging to younger age.

A study conducted by Ganesh et al[18] also found 76% cases of pre eclampsia to be occurring among women aged 20-29 yrs. Comparatively the incidence of pre eclampsia in women aged 20-29 years was 73.7% in the present study.

Duckitt et al[19] study found doubling of incidence of pre eclampsia when women aged > 40 years. The present study had 10% cases aged more than 30 years.

Ramesh et al[20] study found that 21.16years to be mean age for pre eclamptic patients as against 23.56 years among controls. All these factors show preeclampsia to be more common among women in extremes of age group. Younger age women tend to be primigravida whereas older age women have other associated risk factors that increase the incidence of pre eclampsia.

60.6% of women with preeclampsia in this study were primigravida. Abdul Gafur study found primigravida women to be 2.263 times more at risk of developing preeclampsia compared to multigravida women.

The incidence of preeclampsia is more among primigravida compared to multigravida. It is found that women who conceive with same partner tend to have decreased risk compared to women who conceive with a different partner. Likewise women who have miscarried earlier have decreased risk compared to nulligravida.

All these findings suggest that risk of preeclampsia is more among women who are exposed to placental antigen and paternal antigens for the first time. The importance of paternal antigen is shown from the fact that multigravida women who conceive with another partner present with increased risk of preeclampsia.

Also women who have interpregnancy interval of more than 10 years have high risk of preeclampsia. This points to the fact that preeclampsia has a immunological basis in its etiopathogenesis. When the interpregnancy interval is increased they lose out on immunological tolerance and present with increased risk of preeclampsia.

84% of women with pre eclampsia in the present study belong to socioeconomic class 4 and 5. Ramesh et al[20] study showed 80% incidence of pre eclampsia in women belonging to socio economic class 4 and 5.

This is similar to Silva et al[21] study that found lower socioeconomic status to be a risk factor for pre eclampsia. They found the incidence of pre eclampsia to be more common among women with low educational level and poorer income.

Pre eclampsia is increasingly found in developing countries. It is found more common in association with lower socio economic status. The associated factors of malnutrition, poor antenatal care, earlier age of marriage and pregnancy, illiteracy

found among women of lower socio economic status can be attributed to the increased incidence of pre eclampsia in such women.

Ver Luanni et al[22] study found 4% prevalence of preeclampsia. They found that women women who had >8 visits in their antenatal period had lower incidence of preeclampsia with 0.90 being the odds ratio.

The increased risk of preeclampsia in women with lesser antenatal visits could be attributed to the inadequacy in diagnosing and managing pre eclampsia early. Difficulty in accessing health care, decreased educational levels causing decreased awareness of the need for antenatal care could result in poorer attendance at antenatal clinics and lead to missing out on early diagnosis and management of pre eclampsia.

In the present study 15% of women had less than 4 antenatal visits. This group of women with poor antenatal care presented with increased severity of preeclampsia, eclampsia, need for double anti hypertensive drugs and variety of complications.

WHO recommendations advise a minimum of 4 visits in the antenatal period for low risk women. All women are advised to have a monthly visit till 28 weeks of GA, fortnightly visits till 36 weeks of GA, weekly visits till 40 weeks GA for proper and adequate antenatal care.

The presence of preeclampsia in these women was undiagnosed and since they presented with severe preeclampsia and complications they had increased risk of maternal and fetal morbidity. This shows the importance of early diagnosis and treatment of preeclampsia to prevent morbidity and mortality.

The antenatal coverage can be improved by addressing the literacy status of women. Despite adequate healthcare facilities, women in remote hilly areas do not avail the facilities due to lack of awareness. Need to improve awareness among women for antenatal care and risks associated with undiagnosed complicated pregnancies can help a long way in improving the antenatal attendance.

52% women delivered in the early preterm period in the study. 8.4% underwent abortions. 13% deliveries occurred as term gestations. This is similar to Leona et al[23] study that found that risk of delivery before 34 weeks in low risk women was around 1% whereas women with preeclampsia had 60% risk of delivery by 34 weeks.

The increased incidence of preterm births in preeclampsia is because termination of pregnancy being the cure for preeclampsia. So when there is risk of eclampsia, imminent eclampsia, severe complications due to preeclampsia we tend to delvier the baby at the earliest after fetal maturity for the maternal well being. The recommended gestational age of termination of pregnancy in case of severe

preeclampsia is 34 completed weeks of gestation, after administering corticosteroids to accelerate lung maturity.

Many studies have found no benefit in continuing expectant management in pre eclampsia after fetal maturity when there is risk of complications to the mother. But pregnancy can be continued till 37 weeks in cases of non severe preeclampsia and even till 40 weeks in cases of gestational hypertension without proteinuria. Continuing pregnancy beyond the specified cut off gestational age confers no benefit in fetal prognosis. On the contrary it increases risk of maternal and fetal morbidity and mortality.

60.3% of study group had non severe preeclampsia. 6% had eclampsia. Literature says preeclampsia is non preventable but eclampsia is preventable. The incidence of eclampsia in this study group is due to undiagnosed preeclampsia due to poor antenatal visits and non compliance to treatment. Most eclamptic patients in this study were admitted with history of convulsions.

Thornton[24] study showed eclampsia complicating 2.6% of preeclampsia. The risk of eclampsia occurring in preeclamptc mothers according to this study was 1.9. This study reported a fall in incidence of preeclampsia but decline in incidence of preeclampsia did not result in fall in incidence of eclampsia.

Indian incidence of preeclampsia is found to be 8-10%[25] as against the worldwide incidence of 3-5%. Ngwenya[26] reported 1.3% incidence of severe preeclampsia and eclampsia. This study had 26.4% women who were unbooked. 78.5% cases were severely preeclamptic and 21.5% were eclamptic.

In the present study among 20 cases of eclampsia 13 cases (65%) had less than 4 antenatal visits. This shows the association between adequacy of antenatal care and incidence of eclampsia.

50% cases required only a single antihypertensive drug. 18.3% cases required Magnesium sulphate regimen. With increasing severity of preeclampsia patient requirements increased from single drug to multiple drugs and finally magnesium sulphate for prevention or management of eclampsia.

Since 60.3% of cases were non severe preeclampsia, there were a corresponding number of 50% cases requiring only single antihypertensive. Being a high risk group no patient was maintained without drugs.

Assessment of proteinuria and its efficacy in predicting severity of preeclampsia was analysed. Urine albumin on dipstick more than 2+ and urine spot PCR more than 30mg was considered significant proteinuria. Going by this cut off value, 10% of patients in urine spot PCR group versus 34.3% patients in urine albumin group fell under insignificant proteinuria despite being pre eclamptic. This shows that

urine spot PCR is capable of predicting preeclampsia at values earlier than urine albumin, hence proving the superiority over urine albumin as a screening test for preeclampsia.

Definition of preeclampsia no longer includes proteinuria yet proteinuria can be used as a marker to predict women at risk of preeclampsia. Urine spot PCR was able to predict all cases at risk of severe preeclampsia and eclampsia whereas urine albumin could identify only 73.6% and 75% cases respectively. This shows that all women who had elevated urine spot PCR values ended up with some form of complication. Had urine albumin alone been used to screen, almost a quarter of cases could have been undiagnosed.

Phelan K, Brown MA et al studies have also found similar results stressing the need to confirm dipstick proteinuria with spot urine protein creatinine ratio. This was advised as dipstick albumin test was found to have a higher false negative rate.

8.4% cases underwent abortion due to various causes. 40.4% delivered vaginally, 48.6% delivered by cesarean section. Among these majority of vaginal deliveries (49.5%) occurred in preterm period. 73% of cesarean section was among women in their late preterm period. Among term babies 53.9% delivered by cesarean section.

This is similar to a study by Edwards et al[26] that found preeclamptic mothers to be at higher risk of cesarean delivery.

Although preeclampsia per se is not an indication for cesarean section, there is a statistically significant rise in number of cesarean section among preeclamptic mothers. This could be because of the fact that preeclampsia presents with complications, need to minimize the duration of labour, fear of neonatal compromise due to associated risk of IUGR, oligohydramnios, maternal edema and obesity making the patient unfavourable for vaginal delivery.

Among women who underwent abortion, 80% cases were done for preeclampsia and related complications. Most common being severe preeclampsia.

Among the labour natural group, labour set in spontaneously in 27.9% cases. 47.3% cases required induction with prostaglandin gel and the rest required oxytocin induction. The need for induction happens to be severity of preeclampsia, and other associated complications or termination of pregnancy by 37 completed weeks before the onset of labour.

The most common reason for induction of labour was severe preeclampsia occurring in about 32.4% cases and oligohydramnios adding to 18% cases.

Likewise among the LSCS group, the common indication was repeat LSCS done in among 30.1%. The common indication among primigravida was failed induction in about 22%

Complications occurred in 29.3% cases with abruption being the most common in about 13.3%. On analyzing with the predictive value of urine albumin and urine spot P/C ratio, it is found that almost all patients with complications had urine spot P/C >100 whereas the urine albumin levels varied. Complications occurred even in women with non severe preeclampsia with elevated urine spot P/C ratio. However if urine albumin is taken as the criteria in these cases, many complications will go unpredicted in view of patients being classified as non severe category.

Urine spot P/C ratio was elevated >100 in 83 patients, of which 60 patients (72.3%) developed complications. Urine albumin was >2+ in 197 patients of which 64 patients (32.5%) presented with complications. Urine albumin was 4+ in 15 patients of which 11 patients (73.4%) developed complications.

These results show that urine albumin could be elevated in other circumstances as well causing increased false positive values. When the urine albumin cut off is increased, it could lead to missing out of many cases. The reliability of urine albumin for predicting complications is therefore questionable.

However urine spot P/C ratio has better sensitivity and specificity. The results of this study shows that irrespective of the blood pressure reading,, patients presenting with elevated urine spot P/C ratio should be monitored for development

of complications and need strict control of blood pressure. Thus urine spot P/C ratio becomes a better screening test over urine albumin in preeclampsia patients.

The most common complication seen among neonates born to preeclamptic mothers was prematurity in 16.7%. The overall rate of premature deliveries in the study was 85% with only 13% being born as term gestation. The increased incidence of prematurity as explained earlier is due to iatrogenic termination or complications of preeclampsia. But the percentage of premature babies is only 16.7% because 10.9% premature deliveries were complicated by growth restricted fetuses, and the late preterm gestation babies with better weight gain and not requiring NICU admission were excluded while analyzing neonatal outcome. The exclusion was because of the fact that despite being premature, these abbies did not suffer from complications and had better outcome. Including them could alter the result and provide a false good prognosis for neonatal outcome.

54% babies weighed 2-3kg and 16% babies weighed more than 3kg. This is corresponding with 13% term gestation deliveries. Babies born to mothers with severe preeclampsia weighed 1-2kg more commonly and had associated IUGR and other complications.

This is similar to Buchbinder et al study that reported increased rates of preterm deliveries and small for gestational age babies among mothers with preeclampsia.

Another study by Al Mulhim et al found 2.34% stillbirth among preeclamptic mothers as against 3.33% stillbirth rate in the present study.

8.3% babies weighed less than 1kg which is similar to the abortion rate of 8.4%. These babies were excluded while analyzing the neonatal outcome to avoid confounding results.

56% babies required admission in NICU. The admission rate is significantly higher which could be because of the considerably high incidence of preterm deliveries among preeclamptic mothers. The common reason for admission to NICU was low birth weight that occurred in 35.4% babies.

Neonatal outcome showed 18.9% mortality with 10 babies dying in utero and the remaining died in postnatal period. The common cause of death among these neonates was prematurity and associated complications. Despite the fact that preeclampsia promotes accelerated lung maturity and deliveries were conducted after corticosteroid administration, the increased mortality was due to low birth weight, sepsis, and respiratory distress.

Assessing with urine albumin and urine spot P/C ratio of mother we found that urine spot P/C ratio more than 30 predicted poor neonatal outcome in more than 95% cases whereas urine albumin more than 2+ could only be seen associated with

80-90% cases. Neonatal mortality prediction was in 97% of mothers with urine spot P/C ratio >30 and 80% of mothers with urine albumin >2+.

Again the results prove the superiority of urine spot P/C ratio over urine albumin in predicting neonatal outcome. Urine spot P/C ratio also has high false positives for neonatal outcome but it has better sensitivity and specificity over urine albumin. Thus we can conclude that all mothers with elevated urine spot P/C ratio may not have poor neonatal outcome but poor neonatal outcome is almost always associated with elevated urine spot P/C ratio.

This is similar to another study by Mark Brown et al that found significant association between urine spot P/C ratio>30mg/mmol and maternal complication and fetal complication.

The present study found that urine albumin >2+ had 62.3% sensitivity whereas urine spot PCR >30 had 90% sensitivity in predicting preeclampsia. This proves superiority of urine spot PCR over urine albumin.

Another study conducted by Price CP et al comparing urine spot PCR with 24 hour urine protein in prediction of preeclampsia found 69% and 41% sensitivity and 96% and 97% specificity respectively.

Maternal complications occurred in 30% of study group. Of those with complications 98% had urine spot PCR >0.3 whereas only 75% had urine albumin

>2+. Hence elevated urine spot PCR has better sensitivity for predicting complications related to preeclampsia.

Fetal complications occurred in 53.3% of study group. Of this 96% had urine spot PCR >0.3 and 75% had urine albumin >2+. Urine spot PCR is a better predictor for fetal complications also.

SUMMARY:

This study on relationship between urine spot PCR versus urine albumin in predicting severity of pre eclampsia was conducted at Department of OG, Govt Theni Medical College.

A total of 300 preeclamptic mothers were subjected to urine spot PCR and urine albumin and the results were analysed. The study reports are:

- Majority of patients (49.4%) fall in the age group of 20-24 years.
- 60.6% of the study group were primigravida.
- 84% of women belonged to lower socioeconomic status, with 47% belonging to class 5 socioeconomic status.

- 15% women had less than 4 antenatal visits.
- 52% women delivered in 34-37 weeks of gestation and 8.4% underwent abortion.
- 60.3% had non severe preeclampsia and 6.6% suffered from eclampsia.
- 50% cases required single drug and 18.3% cases required treatment with magnesium sulphate.
- 34.3% had <2+ urine albumin, 43% had 2+ urine albumin, 17.7% had 3+ urine albumin, 5% had 4+ urine albumin on dipstick.
- 10% patients had <0.3 urine spot PCR, 62.4% had spot P/C ratio of 30-100mg/mmol, 17.6% had spot P/C ratio >100mg/mmol.
- Urine spot P/C had 100% prediction of severe preeclampsia and eclampsia whereas urine albumin had only 73.6% and 75% prediction respectively.
- 8.3% underwent abortions, 40.4% delivered vaginally and 48.6% delivered by cesarean section.
- Labour was spontaneous in 34.7% cases and induced in 63.3% cases.
- Induction of labour was done in 32.3% cases due to severe preeclampsia.

- LSCS was done in 48.6% cases, the common indication being repeat LSCS in 30% cases.
- 21.7% LSCS was due to failed induction, which was common among primigravida.
- 13.3% developed abruption, 6.7% developed AP eclampsia, and 70.7% cases were uncomplicated.
- 72.3% women with urine spot P/C ratio >100 and 32.5% women with urine albumin >2+ presented with maternal complications.
- 56% babies developed various complications and needed admission in NICU.
- 54% babies weighed 2-3kg and 8.3% babies weighed less than 1kg at delivery.
- Stillbirth rate was 3.3% in study sample.
- Neonatal mortality rate was 14% in the study sample.
- Neonatal complications occurred in 62% women with elevated urine spot P/C ratio and 52% women with urine albumin >2+.

CONCLUSION:

- Preeclampsia is a disorder affecting multiple organ systems specific to pregnancy.
- It is important cause of maternal and fetal morbidity and mortality.

- Increasing proteinuria is associated with increasing severity of preeclampsia and its complications.
- The urine spot protein creatinine ratio is a effective alternative to 24 hour urine protein and is much superior to urine albumin in predicting severity of pre eclampsia.
- Urine spot P/C ratio has better sensitivity and specificity in predicting severity of preeclampsia and maternal and fetal outcome.
- Urine spot P/C ratio is simple, easy and convenient alternative to the tedious 24 hour urine protein estimation.
- Urine spot P/C can be done at all health centre levels as it does not require much technicalities.
- Various studies have proven the efficacy of this test and included it in the battery of investigations to be done for a preeclamptic mother.
- Increasing urine spot P/C ratio is a marker of worsening spectrum of preeclampsia.

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PROFORMA

Case No:

Name: Age: IP NO:

Address:

Occupation:

Education status:

Socioeconomic status:

Obstetric code:

Booking status:

LMP: EDD:

PRESENTING COMPLAINTS:

c/o pain abdomen

c/o bleeing pv

c/o draining pv

ability to perceive fetal movements

c/o epigastric pain, headache, nausea, vomiting, blurring of vision

h/o convulsions

OBSTETRIC HISTORY:

Details of previous pregnancy:

Parity: Live:

Sex:

Mode of delivery:

If LSCS, indication:

LCB:

Birth weight:

Details of present pregnancy:

No of antenatal visits:

Diagnosis of PIH at:

PAST HISTORY:

h/o chronic hypertension

h/o gestational diabetes mellitus

h/o renal disorder

h/o liver disorder

GENERAL EXAMINATION:

O/E pt conscious

anemic

Icterus

Pedal edema

PR:

BP:

PER ABDOMINAL EXAMINATION:

Fundal height:

Fetal heart sounds:

Contractions:

Presenting part:

LABORATORY INVESTIGATIONS:

CBC:

RBS:

Urea:

Creatinine:

LFT:

Urine albumin:

Urine spot P/C ratio:

DETAILS OF FOLLOW UP:

Mode of delivery:

Period of gestation:

Onset of labour:

If induced, mode of induction:

Indication for induction:

If LSCS, indication for LSCS:

MOTHER DETAILS:

Presence of RP clots:

Urine output:

CVT:

DVT:

HELLP:

PPCM:

Pulmonary edema features:

TREATMENT DETAILS:

Labetalol:

Nifedipine:

Inj.MgSo4:

BABY DETAILS:

Sex of baby:

Birth weight:

Gestational age:

NICU admission:

If admitted, reason:

APGAR:

On discharge, baby status:

KEY TO MASTER CHART:

GA: gestational age

SE: socioeconomic status

Professionals

1- Graduates

2- Skilled worker

3- Semiskilled worker with monthly wage

4- Semiskilled worker with daily wage

ANC: Antenatal care – no of antenatal visits

Column 12:

L – T.Labetalol.

N- T.Nifedipine,

M- Inj.MgSO4

Column 13: Maternal complications

A- Abruption

C- Cortical vein thrombosis

D-Deep vein thrombosis

CM-peripartum cardiomyopathy

E-antepartum eclampsia

H-HELLP syndrome

PE-pulmonary edema

PP-Postpartum eclampsia

PRES-posterior reversible encephalopathy syndrome

Column 14: Onset of labour

A- Artificial rupture of membranes with oxytocin induction

P-prostaglandin gel induction

S-spontaneous onset

Column 15: Indications for induction

A- Abruption

E- eclampsia

G- intra uterine growth restricted fetus

IUD- intrauterine death

O-oligohydramnios

P-Premature rupture of membranes

S-Severe preeclampsia

T-Term gestation

Column 16: Indications for LSCS

A-abruption

B-breech

CPD-cephalopelvic disproportion

E- eclampsia

FI- Failed induction

FD- Fetal distress

IUGR- intra uterine growth restricted fetus

RPT- repeat LSCS

Column 17: Mode of delivery

F- outlet forceps

LN – labour natural

LSCS- lower segment cesarean section

SE- spontaneous expulsion

V- vacuum

Column 20: Fetal outcome

P-prematurity

G- IUGR fetus

FD- fetal distress

D-Neonatal Death of baby

IUD – intra uterine death

Ref. No. 2643/ME1/16

Government Theni Medical College
Theni. Dated: 07.06.2016

Institutional Ethical Committee:

Convenor:

Dr. T. Thirunavukkarasu, M.D., D.A.,
Dean
Govt. Theni Medical College
Theni

Sub: Medical Education – Govt. Theni Medical College,
Theni – Ethical Committee – Minutes – Communicated – Reg.

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The Ethical Committee Meeting of the Govt. Theni Medical College, Theni was held at 12.00 noon on 03.06.2016 at Conference Hall, Near Dean's Chamber, Government Theni Medical College, Theni.

The following Members of the Committee have attended the Meeting.

1.	**Convener**	:	**Dr. T. Thirunavukkarasu, M.D., D.A., Dean**
2.	**Member Secretary**	:	**Dr. M. Ilangovan, M.S., Deputy Superintendent**
3.	**Members**		
	Professor of Medicine	:	**Dr. P. Purushothaman, M.D.,**
	Professor of Surgery	:	**Dr. R. Murugesan, M.S.,**
	Professor of Obs. & Gynaec.	:	**Dr. Thangamani, M.D., O.G.,**
	Professor of Micro Biology	:	**Dr. K.M. Mythreyee, M.D.,**
4.	**Chairman (Private Consultant)**	:	**Dr. Paulraj, M.D.,** Ramya Clinic, Periyakulam Road, Theni.
5.	**Lawyer**	:	**Thiru.K.Murugesan, B.Com., B.L.,** S/o.Kamaraj, Ambedkar Nagar, Varusanadu, Theni District.
6.	**Sociologist**	:	**Sr. Anaestescia** Director, Jeevan Jothi Hospital Community Care Centre, Periyakulam Road, Kailasapatti, Theni Dist.
7.	**Public**	:	**Mr. P. Deenadhayalan, M.A.,** Land Lord, Koduvilarpatti, Theni District.